

Phase transitions and membrane stiffness in a class of asymmetric heterogeneous fluid membranes

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We propose a minimal model for miscibility phase transitions (MPTs) in a class of asymmetric two-component heterogeneous fluid membranes at equilibrium that generically display both first and second order MPTs, controlled by the interplay of asymmetry and heterogeneity. In the vicinity of the MPTs, the membrane fluctuations are generally enhanced. However, the degree of enhancement is found to depend sensitively on the asymmetry-heterogeneity coupling. We argue that experimental measurements of the membrane fluctuations at the MPTs should provide physical information about the forms of the asymmetry-heterogeneity couplings.

Introduction:- Miscibility phase transitions (MPTs) in heterogeneous membranes at equilibrium are a subject of intense research. Symmetric model lipid bilayers (i.e., lipid bilayers with inversion symmetry) undergo an MPT from a high temperature (T) homogeneous phase to a low temperature coexistence phase of liquid disordered and liquid ordered domains [1]. Extensive experimental results suggest that the MPTs in symmetric model membranes are generically second order in nature, belonging to the two-dimensional (2D) Ising universality class [2]. In contrast to their symmetric counterparts, model heterogeneous asymmetric membranes are distinguished by the lack of inversion symmetry and their composition dependent *local spontaneous curvatures* C_0 , that affect the coarsening dynamics and equilibrium shapes [3]. Nonetheless, a general understanding of how asymmetry affects the nature of the associated MPTs is still lacking.

In this Letter we theoretically describe how the interplay of asymmetry and inhomogeneity in a fluid membrane affects the phases and the associated MPTs. To this end, we construct a generic minimal model in the spirit of coarse-grained Ginzburg-Landau approaches in terms of the local composition inhomogeneity and curvature as the relevant thermodynamic variables. In order to focus on the essential physical aspects of the problem, we consider a tension-less single fluid membrane with two-component heterogeneities. For the sake of simplicity and generality, we do not distinguish between bilayer membranes and monolayer amphiphilic films [4, 5]. Apart from its phenomenological significance, our model is a good candidate to theoretically study 2D critical behaviour on a fluctuating membrane.

Our model displays a complex phase diagram with a rich variety of phases and MPTs, including both second order transitions through critical (CP) and tricritical (TP) points, and first order transitions. Coupling constants that parametrise C_0 in our model appear as control parameters. Associated membrane conformation

fluctuations are generically enhanced; however, the degree of enhancement can be controlled by these tuning parameters. Furthermore, the magnitude and sign of C_0 in the ordered, phase-separated state in our model can be tuned at a given T by controlling the parameters. Our results demonstrate the importance of measuring the membrane fluctuations in experimental characterization of MPTs in asymmetric membranes. Our model is designed to capture the essential physical consequences of nonlinear asymmetry-inhomogeneity interactions and has few biological or microscopic details. Nonetheless, considering the generality of our model, we expect the basic features of our results, e.g., the significance of nonlinear asymmetry-inhomogeneity couplings on the MPT and the nature of the associated membrane fluctuations should be relevant for non-linear curvature-composition interactions in generic experiments on heterogeneous membranes and nonlinear aspects of *lipid sorting* near phase transitions in bilayer lipid membranes [6].

Construction of our model:- We describe inhomogeneity by a single composition field $\phi(\mathbf{x})$. Physical interpretations of ϕ depend on specific systems. For instance, for an amphiphilic monolayers separating two distinct solvents (e.g., oil and water), ϕ is the local difference between the concentrations of the two types of lipids A and B; where as for lamellae or vesicles made of bilayer membranes, it is the local composition difference between the two layers of the bilayer [4, 5], or, for a diffusing chemical in a membrane, e.g., in *echinocytosis* of red blood cells, it is the local density fluctuations of the diffusing molecules [5, 7, 8]. Naturally, the underlying microscopic mechanisms behind the inversion asymmetry differ from one system to another, e.g., different intrinsic spontaneous curvatures of the two components in a two-component monolayer, the composition difference between the inner and the outer layers [5], or, the preference of the intercalated molecules for the tilted configurations of their surrounding phospholipids [7] in a bilayer. We adopt the standard Ginzburg-Landau free energy functional for binary mixtures [4, 9, 10], useful near a critical point. We consider $C_0(\phi)$ to be a generic nonlinear function of ϕ [11], and for purposes of illustration assume $C_0(\phi) = -C_0(-\phi)$, so that A and B-

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excess regions have opposite local curvatures (assuming an amphiphilic membrane); see Fig. 1. Next, assume the

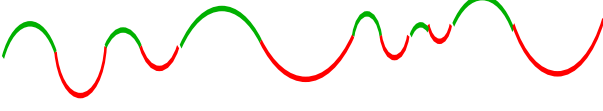


FIG. 1: (Color online) Schematic diagram of our model heterogeneous amphiphilic membrane; red (curved upward)/green (curved downward) segments represent A-excess/B-excess regions with opposite C_0 , respectively.

standard Helfrich-Canham curvature energy for a tensionless [12], zero thickness [13] membrane, parametrised by the bending modulus κ and a single-valued height field $h(\mathbf{x}, t)$, of the form $\kappa[\nabla^2 h - C_0(\phi)]^2$ in the Monge gauge [14], for planar fluid membrane configurations. Evidently, the free energy functional \mathcal{F} is invariant under $h \rightarrow -h$ together with $\phi \rightarrow -\phi$. We have then,

$$\mathcal{F} = \int d^d x \left[\frac{r}{2} \phi^2 + \frac{1}{2} (\nabla \phi)^2 + \frac{u}{4!} \phi^4 + \frac{v}{6!} \phi^6 + \frac{\kappa}{2} (\nabla^2 h)^2 + \lambda \phi \nabla^2 h + \lambda_1 \phi^3 \nabla^2 h \right], \quad (1)$$

truncating to the lowest order nonlinear terms. Here $r \sim (T - T_c)$, T_c being the mean-field (MF) critical temperature without any coupling to h . Coupling constants $u > 0$ and $v > 0$ determine the strength of the local lipid-lipid interactions. The v -term in \mathcal{F} is required for thermodynamic stability as we discuss below. The absence of invariance under the inversion of h for a given ϕ enforces asymmetry in the model [7, 15]. We have $C_0(\phi) = -(\lambda \phi + \lambda_1 \phi^3)/\kappa$. Notice that the individual signs of λ and λ_1 are arbitrary: Signs of both λ, λ_1 may be flipped by redefining $h \rightarrow -h$, or, $\phi \rightarrow -\phi$. The sign of the product $\lambda \lambda_1$, however, cannot be transformed away. In fact, the signature of $\lambda \lambda_1$ pertains to important microscopic material properties: $\lambda \lambda_1 > 0$ implies that the contributions of the microscopic interactions between curvature and three or one lipid molecules to \mathcal{F} are mutually cooperative; on the other hand for $\lambda \lambda_1 < 0$, these microscopic interactions are mutually competing [16]. In the latter case, for $\lambda \sim -\lambda_1 \phi^2$ the two contributions roughly cancel out. This has strong ramifications on the MPTs, as we find below. On dimensional ground in 2D, following the arguments in Ref. [4], $\lambda n_0 \sim \kappa H_0$, $\lambda_1 n_0^3 \sim \kappa H_0$, where n_0 is the mean concentration and H_0 is a typical microscopic (local) curvature, yielding $\lambda \sim \kappa H_0 \xi_0^2$, $\lambda_1 \sim \kappa H_0 \xi_0^6$ [17], with ξ_0 being the microscopic correlation length scale. Taking $\xi_0 \sim 10^{-9} m$ [4], $\kappa \sim 100 k_B T$ (k_B is the Boltzmann constant) and $H_0 \sim 10^6 m^{-1}$, we find $\lambda \sim 10^{-10} k_B T m$, $\lambda_1 \sim 10^{-46} k_B T m^5$.

Mean-field analysis:- We now construct a mean-field theory (MFT) [10] by minimizing \mathcal{F} with respect to (constant in MFT) twice the negative of the mean curvature

$C = \nabla^2 h$ and order parameter $m = \phi$. We find

$$rm + \lambda C + 3\lambda_1 m^2 C + \frac{u}{3!} m^3 + \frac{v}{5!} m^5 = 0, \quad (2)$$

$$\kappa C + \lambda m + \lambda_1 m^3 = 0. \quad (3)$$

For symmetric membranes $\lambda = 0 = \lambda_1$. Hence, $C = 0$ for all T and $m = 0$ for all $T \geq T_c$ and $\phi = m \neq 0$ for all $T < T_c$ with a second order transition at T_c , belonging to the Ising MF universality class. Our results for an asymmetric membrane are far richer in behavior: Eq. (3) shows that for an asymmetric membrane in the ordered phase with a non-zero m (a) $C \neq 0$, and (b) the signatures of C , being dependent on that of m not surprisingly, are opposite in the A or B rich domains in the ordered phase. Now eliminate C in Eq. (2) by using Eq. (3) to construct an *effective* Landau free energy \mathcal{F}_e :

$$\mathcal{F}_e = \frac{\tilde{r}}{2} m^2 + \tilde{u} m^4 + \tilde{v} m^6, \quad (4)$$

where $\tilde{r} = r - \frac{\lambda^2}{\kappa}$, $\tilde{u} = \frac{u}{4!} - \frac{\lambda \lambda_1}{\kappa}$ and $\tilde{v} = \frac{v}{6!} - \frac{\lambda_1^2}{2\kappa}$. Parameter \tilde{r} defines effective MF critical temperature $\tilde{T}_c = T_c + \frac{\lambda^2}{\kappa}$. Effective coupling constants \tilde{u} and \tilde{v} can be either positive, negative or zero, separately or together. We assume $\tilde{v} > 0$ always. Then, \mathcal{F}_e is identical to that for the normal superfluid transition in liquid helium mixtures [18].

Free energy (4) allows for both first and second order transitions in the system, depending upon the relative magnitudes and signatures of \tilde{r}, \tilde{u} [10]: (i) By construction when $\tilde{r} = 0$, $\tilde{u} > 0$, $\tilde{v} > 0$, \mathcal{F}_e admits a second order phase transition for m belonging to the MF Ising universality class. This holds for all λ, λ_1 , such that $\lambda \lambda_1 < 0$, and also for $\lambda \lambda_1 > 0$ as long as $\tilde{u} > 0$, (ii) For sufficiently large $\lambda \lambda_1 > 0$, $\tilde{u} < 0$ and the \tilde{v} -term is then necessary for thermodynamic stability. For this, the system undergoes a first order phase transition with $m = \pm \sqrt{\frac{|\tilde{u}|}{2\tilde{v}}} \neq 0$ at $\tilde{r}^* = 4\tilde{u}m^2 - 6\tilde{v}m^4 = \frac{\tilde{u}^2}{2\tilde{v}} > 0$, yielding a transition temperature $\tilde{T}_c^* = \tilde{T}_c + \frac{\tilde{u}^2}{2\tilde{v}}$. This meets the second order transition at $\tilde{r} = 0$, $\tilde{u} = 0$, which defines a TP. The corresponding MF critical scaling exponents belong to the MF TP universality class [10].

For an asymmetric membrane, $C = 0$ in the disordered phase and in general $C = C(m) = -(\lambda m + \lambda_1 m^3)/\kappa \neq 0$ in the ordered phase. Hence, with equal and opposite C in the A and B-rich domains, $C(m)$ changes sign as m changes sign in the ordered phase. Variation of $C(m)$ across the transition temperature, that originates in the corresponding T dependence of m , may be used to delineate the nature of the transition: Below CP or TP, it grows continuously from zero as T decreases; in contrast, it displays a jump, controlled by the jump in m , across a first order transition [19]. In addition, the magnitude and sign of C may be tuned in the ordered phase by controlling λ and λ_1 : $C = 0$ along the *zero curvature line* $\lambda + \lambda_1 m^2 = 0$ in the ordered phase. This requires $\lambda \lambda_1 < 0$ and hence $\tilde{u} > 0$.

Effect of small fluctuations:- Consider now (small) fluctuations in the disordered phase ($r > 0$). Retaining terms up to the harmonic order in \mathcal{F} and integrating ϕ in the partition function $\mathcal{Z} = \int \mathcal{D}h \mathcal{D}\phi \exp[-\mathcal{F}]$ ($k_B T = 1$) yields a wavevector \mathbf{q} -dependent effective bending modulus

$$\kappa_e = \kappa - \lambda^2/(r + q^2) \approx \kappa - \frac{\lambda^2}{r} = \kappa_0 < \kappa \quad (5)$$

for $q \rightarrow 0$ at $r > 0$. Thus, $\kappa_e(q = 0) = 0$ at $\kappa = \lambda^2/r$ or $\tilde{r} = 0$. Similarly in the ordered phase define $\phi = m + \psi$, $\nabla^2 h = C + \delta c$, where m and C are the solutions of Eqs. (2) and (3) in the ordered state and $\langle \psi \rangle = 0 = \langle \delta c \rangle$. Expand \mathcal{F} to the bilinear order in ψ and δc . The terms linear in ψ and δc vanish, since m and C minimise \mathcal{F} in the ordered phase. We obtain

$$\begin{aligned} \mathcal{F}_o = & \int d^d x \left[\frac{r}{2} \psi^2 + \frac{1}{2} (\nabla \psi)^2 + \frac{6u}{4!} m^2 \psi^2 + 15 \frac{v}{6!} m^4 \psi^2 \right. \\ & \left. + \frac{\kappa}{2} (\delta c)^2 + \lambda \psi \delta c + 3\lambda_1 m^2 \psi \delta c \right]. \end{aligned} \quad (6)$$

Then, proceeding as before and integrating out ψ , we obtain an effective free energy functional for the ordered phase that depends on δc only, and thence, assuming $m^2 = -3!(r/u)$ to the lowest order in λ, λ_1 in the ordered phase, κ_e in the ordered phase given by

$$\kappa_e(q) = \kappa - \frac{(\lambda + 3\lambda_1 m^2)^2}{-2r + q^2} \leq \kappa. \quad (7)$$

In particular, along the zero spontaneous curvature line given by $\lambda + 3\lambda_1 m^2 = 0$, $\kappa_e = \kappa$. Else, $\kappa_e < \kappa$.

Role of the anharmonic fluctuations:- Anharmonic fluctuation contributions to κ_e , neglected above, should dominate near CP, due to the large (formally diverging in the thermodynamic limit) critical fluctuations. As above, we need to integrate over ϕ (now retaining the anharmonic terms in \mathcal{F}) in \mathcal{Z} near CP and obtain an effective free energy functional for h , and thence extract κ_e from there. Due to the anharmonicity, an exact integration is ruled out; instead perturbative calculations based on renormalisation group (RG) calculations should be employed to systematically handle the large (formally diverging in the thermodynamic limit (TL)) critical point fluctuations [10, 20]. This is a technically challenging task. It is, however, easier to calculate the height fluctuation correlator $\langle |h_{\mathbf{q}}|^2 \rangle_\phi$ for a given configuration of ϕ . This is given by

$$\langle |h_{\mathbf{q}}|^2 \rangle_\phi = \int \mathcal{D}h \exp[\mathcal{F}] \frac{1}{Z_\phi}, \quad (8)$$

where $Z_\phi = \int \mathcal{D}h \exp[-\mathcal{F}]$. Equation (8) yields

$$\langle |h_{\mathbf{q}}|^2 \rangle_\phi = \frac{1}{\kappa q^4} + |(\lambda \phi + \lambda_1 \phi^3)_{\mathbf{q}}|^2 \frac{1}{\kappa^2 q^4} > \frac{1}{\kappa q^4}. \quad (9)$$

Thus, $\langle |h_{\mathbf{q}}|^2 \rangle_\phi$ is always enhanced in the presence of a given arbitrary configuration of ϕ . Hence, the height

fluctuation correlator $\langle h_{\mathbf{q}}|^2 \rangle$, averaged over all possible configurations of ϕ with respect to the Boltzmann distribution determined by \mathcal{F}_0 should be enhanced by ϕ fluctuations. Thus, $\kappa_e < \kappa$ necessarily.

Actual enumeration of κ_e can only be done perturbatively. This is conveniently done by naively expanding \mathcal{Z} in powers of (assumed small) λ, λ_1, u . This immediately yields,

$$\kappa_e(q) = \kappa - \langle |\lambda \phi + \lambda_1 \phi^3|_{\mathbf{q}}^2 \rangle \quad (10)$$

to $O(u^0)$. The last term in the rhs of (10) involves calculation of higher order correlation functions of ϕ , a difficult task by itself. In order to get a quantitative sense of the nature of the correction to κ in (10), we resort to the Hartree approximation [10] and replace ϕ^3 in (10) by $3\langle \phi^2 \rangle \phi$ (this amounts to ignoring higher-order connected correlators of ϕ). This yields

$$\kappa_e(q) = \kappa - (\lambda + \lambda_1 \langle \phi^2 \rangle)^2 \langle |\phi_{\mathbf{q}}|^2 \rangle, \quad (11)$$

where $\langle \phi^2 \rangle = \int \frac{d^d q}{(2\pi)^d} \langle |\phi_{\mathbf{q}}|^2 \rangle$ in d -dimensions that should be obtained self-consistently. In (11), contributions to κ_e from connected higher order correlations of ϕ are ignored. Ignoring self-consistency and noting that under spatial rescaling $\mathbf{x}' = b\mathbf{x}$, coupling constants λ and λ_1 and field ϕ scale as $b\lambda$, $b^{3-d}\lambda_1$ and $b^{(2-d)/2}\phi$, all the contributions to the corrections for κ in (11) are equally relevant at $2d$ in a scaling sense. For a system of linear size $L \sim 1/q_0$,

$$\begin{aligned} \Delta \kappa_e(q_0) &= \kappa_e(q_0) - \kappa \sim -\frac{(\lambda + \lambda_1 \langle \phi^2 \rangle)^2}{\tilde{r} + q_0^2} \rightarrow -\frac{(\lambda + \lambda_1 \langle \phi^2 \rangle)^2}{q_0^2} \\ &\sim -(\lambda + \lambda_1 \langle \phi^2 \rangle)^2 L^2, \end{aligned} \quad (12)$$

near the critical point of MPT. Evidently, for a large enough L , $\kappa_e(L) = 0$. This allows us to define a *persistence length* ζ_h for the membrane conformation fluctuations by $\kappa_e(\zeta_h) = 0$, giving

$$\zeta_h \sim \sqrt{\frac{\kappa}{[\lambda + \lambda_1 \langle \phi^2 \rangle]^2}}. \quad (13)$$

Thus, if λ and λ_1 are of the same sign, then $\Delta \kappa_e$ is increased in magnitude and ζ_h is decreased. In contrast, when they are of opposite signs, $\Delta \kappa_e$ is reduced and ζ_h is enhanced; see Fig. 2 for schematic variation of ζ_h with λ_1 for a fixed $\lambda > 0$. Accordingly, the membrane fluctuates more for $\lambda\lambda_1 > 0$ (“more soft”) than for $\lambda\lambda_1 < 0$ (“less soft”). Since λ and λ_1 are free parameters in our model, it is possible to make $\Delta \kappa_e$ vanishingly small by choosing $\lambda \sim -\lambda_1 \langle \phi^2 \rangle$. Within our analysis, this makes ζ_h diverging [21]. The corresponding anharmonic fluctuation corrections to $\kappa_e(q)$ in the ordered phase close to CP to the lowest order in λ, λ_1

$$\kappa_e(q) \approx \kappa - \frac{(\lambda + 3\lambda_1 m^2 + 3\lambda_1 \langle \psi^2 \rangle)^2}{-2r + q^2}, \quad (14)$$

where $\langle \psi^2 \rangle = \int \frac{d^d q}{(2\pi)^d} \langle |\psi(\mathbf{q})|^2 \rangle$. Thus, $\Delta \kappa_e < 0$ in general; its magnitude may be controlled (can be increased

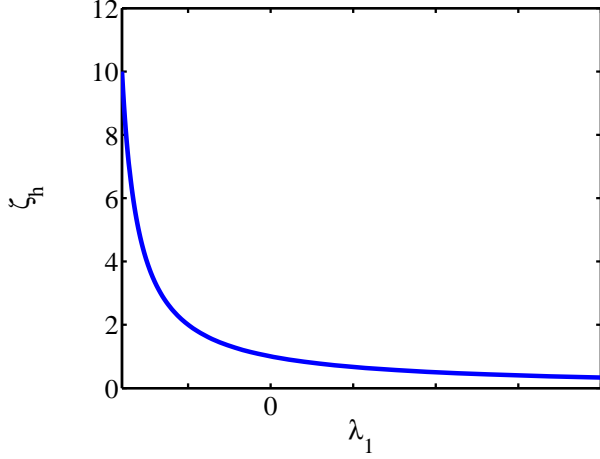


FIG. 2: Schematic variation of ζ_h with λ_1 for a fixed $\lambda > 0$. Clearly ζ_h is large for $\lambda\lambda_1 < 0$ and gets smaller as $\lambda\lambda_1$ increases and becomes positive.

or decreased) by tuning the magnitudes and signs of λ, λ_1 as for above CP. In contrast, across a first order transition, fluctuation effects should be negligible. Hence, by using (7)

$$\Delta\kappa_e(q = q_0) = -\frac{(\lambda + 3\lambda_1 m^2)^2}{\tilde{r}^* + q_0^2}, \quad (15)$$

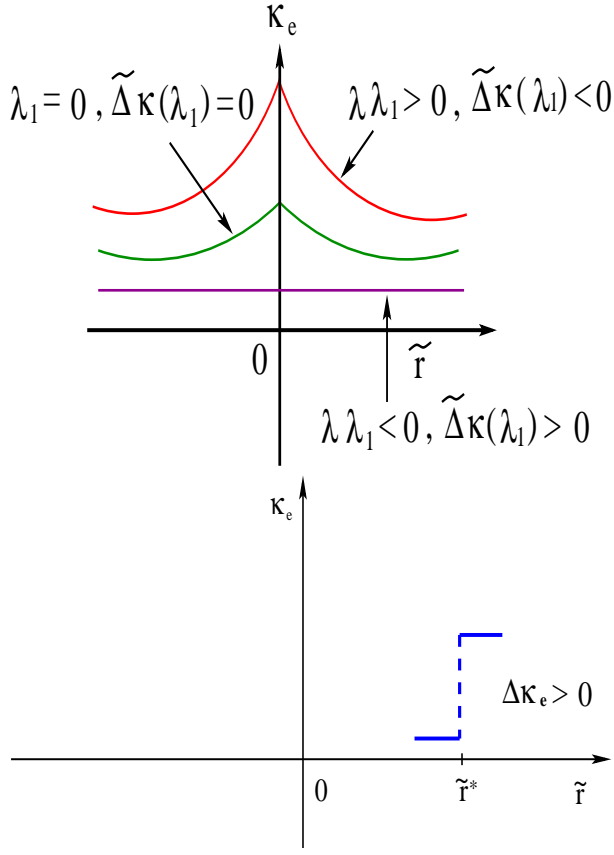
$m^2 = 0, |\tilde{u}|/(2\tilde{v})$ in the disordered and ordered phase respectively. Hence, there is a jump in κ_e across a first order transition. For a first order transition, $\lambda\lambda_1 > 0$, and hence, both λ and λ_1 are either positive or negative. Thus, $\Delta\kappa_e(q = q_0) < 0$ necessarily for a first order transition. Further, (15) reveals a jump in κ_e , due to the jump in m . Overall, thus we see that the harmonic composition fluctuation contributions to κ_e always reduces κ_e . The corresponding anharmonic contribution may further reduce κ_e , or, may partly suppress reduction of κ_e by the composition fluctuations at the harmonic order. This can be argued heuristically from the form of (1). When $\lambda_1 = 0$, Gaussian fluctuations of ϕ is known to soften the membrane as evident from (5), due to a possible reduction in free energy in a given bent configuration by adjusting ϕ -fluctuations. Noting that for $\lambda\lambda_1 < 0$, free energy reduction due to the fluctuations of ϕ at the Gaussian order is compensated by a free energy cost due to the λ_1 -term. These two contributions (1) should balance when $\lambda \sim -\lambda_1\phi^2$. This explains the mutually cooperative (competing) nature of the contributions to κ_e from the composition fluctuations at the harmonic and anharmonic orders for $\lambda\lambda_1 > (<)0$.

Considering that κ has no significant T -dependences, measurements of κ_e as a function of T yield information about λ and λ_1 . For instance, for a second order MPT, measuring κ_e versus T above CP and using (5) yields λ . Similar procedure below CP, now with the knowledge of m^2 (use MFT results or measure experimentally) yields λ_1 . Similarly, across a first order transition measuring

$\Delta\kappa_e$ as a function of $T > \tilde{T}_c^*$ yields λ^2 ; see Eq. (15). Measuring the same quantity for $T < \tilde{T}_c^*$ with the knowledge of λ obtained as above then yields $\lambda_1 m^2$. Use then $m^2 = |\tilde{u}|/(2\tilde{v})$ (or measure it separately) below the MPT to obtain λ_1 . For a first order transition, $\lambda\lambda_1 > 0$, and hence, both λ and λ_1 are either positive or negative. We classify the membrane fluctuations near the associated MPTs according to the nature of the corresponding MPTs - first order ($\lambda\lambda_1 > 0, \tilde{u} < 0$), second order with cooperative asymmetry-heterogeneity interactions ($\lambda\lambda_1 > 0, \tilde{u} > 0$, “membrane more soft”) and second order with competing asymmetry-heterogeneity interactions ($\lambda\lambda_1 < 0, \tilde{u} > 0$, “membrane less soft”). In the second and third cases, $\tilde{\Delta}\kappa = \kappa_e(\lambda_1) - \kappa_e(\lambda_1 = 0)$ is negative and positive, respectively. Thus, measurements of $\tilde{\Delta}\kappa$ yield information about the sign of $\lambda\lambda_1$. Notice that at the level of our analysis based on the Hartree approximation, the last two cases differ only in the quantitative degree of membrane fluctuation enhancement. Variations of κ_e with \tilde{r} are schematically shown in Fig. (3) across second order and first order transitions.

Phase diagrams:- Our results are summarised in schematic phase diagrams (4-5) below. In Fig. (4) different types of transitions displayed by our model (within our MF analysis) and the corresponding changes in κ_e across the transitions are marked in the $\tilde{r} - \lambda$ plane ($\lambda_1 > 0$). The locations of TP given by the condition $\tilde{u} = 0$, and the line of zero spontaneous curvature, given by $C(m) = 0$ for particular choices of λ, λ_1 (in the ordered phase), are shown. Figure (5) shows what type of MPTs are expected for a given set of (λ, λ_1) as temperature is lowered. The two (curved) lines of TP are given by $\tilde{u} = 0$, or, $\lambda\lambda_1/\kappa = u/4!$. For $\lambda\lambda_1 > u\kappa/4!$ (regions marked A), $\tilde{u} < 0$, and hence corresponds to first order transitions. In regions marked B, on the other hand, $\tilde{u} > 0$ with $\lambda\lambda_1 > 0$ and hence they correspond to second order transitions with a very soft membrane across the transition. In contrast, $\tilde{u} > 0$ with $\lambda\lambda_1 < 0$ in regions marked C; these describe second order transitions with “less soft” membranes across the transitions.

Summary and outlook:- Thus, we show how the interplay between composition and asymmetry determine the ensuing phases and phase transitions, and generic suppression of membrane fluctuations in asymmetric membranes, which are markedly more complex than symmetric membranes. Furthermore, the degree of enhancement can be controlled by the coupling constants that define the coupling between the local asymmetry and heterogeneity. Since λ, λ_1 have very different dependences on ξ_0 , performing experiments on model asymmetric heterogeneous membranes with different sizes of the constituent lipid molecules should be a promising route to test our results experimentally. For instance, if ξ_0 changes by 10%, λ, λ_1 change by about 20% and 60%, respectively. Thus shows that by varying ξ_0 , the effective stiffness of an asymmetric membrane can vary significantly. Our model demonstrates the significance of the sign of the product $\lambda\lambda_1$. Complementary to our analysis above,



phases and phase transitions in (1) may also be tested in numerical simulations of suitably constructed equivalent lattice-gas based 2D lattice Hamiltonian with an Ising spin degree of freedom S_{ij} , a discrete analogue of $\phi(\mathbf{x})$ here ((i, j) is the coordinate of a point on the 2D lattice), and a discretised local curvature of the lattice h_{ij} (see, e.g., Ref. [22]). Discrete analogues of the λ - and λ_1 -terms may be constructed by coupling S_{ij} with h_{ij} appropriately. Additionally, atomistic models for asymmetric lipid bilayers that may correspond to the coarse-grained free energy (1) may be constructed by introducing local many-body interactions involving three atoms (or interaction sites) and the curvature and controlling its sign. In turn, knowledge about $\tilde{\lambda}$ should yield useful information about the underlying microscopic interactions. We look forward to synthesis of model asymmetric lipid membranes which may be used in experiments by standard, e.g., fluorescence, methods (see, e.g., Ref. [2]) to study the properties elucidated above. Membrane fluctuations and their dependences on λ, λ_1 may be inves-

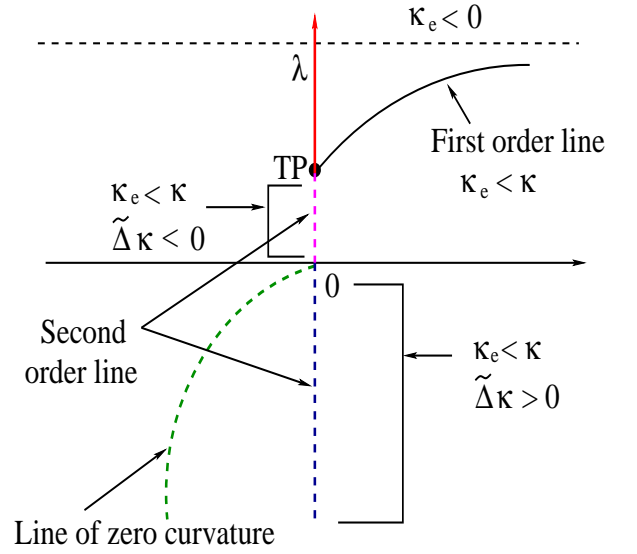


FIG. 4: (Color online) Schematic phase diagram in the $\tilde{r} - \lambda$ plane ($\lambda_1 > 0$). First and second order lines with the change in κ_e across the transitions and TP are marked. A line of zero curvature is schematically drawn.

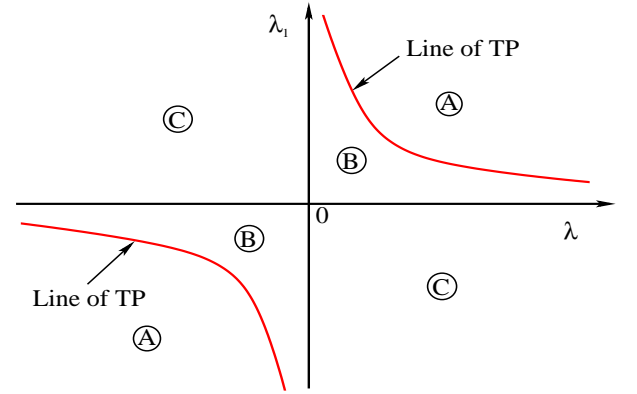


FIG. 5: (Color online) The nature of transitions in the different regions of the $\lambda - \lambda_1$ plane: Systems with λ, λ_1 belonging to the regions marked A, B and C undergo first, second ($\lambda\lambda_1 > 0, \tilde{u} > 0, \tilde{\Delta}\kappa < 0$) and second ($\lambda\lambda_1 < 0, \tilde{u} > 0, \tilde{\Delta}\kappa > 0$) order transitions respectively; red curved lines are the locations of TPs ($\tilde{u} = 0$).

tigated by standard experimental methods, e.g., optical interferometric methods [23]. The number of tunable parameters in our model is similar in number in analogous models for symmetric inhomogeneous membranes (see, e.g., Ref. [24]). Nevertheless, the MPTs in our asymmetric inhomogeneous model membranes are starkly different from those for symmetric ones. This highlights the crucial role of asymmetry.

Our results are strongly related to the symmetry properties of (1), i.e., $C_0(\phi) = -C_0(-\phi)$, or, equivalently, symmetry under the joint inversion $(h, \phi) \rightarrow (-h, -\phi)$. If the molecular curvatures of lipid molecules A and B are different, then this symmetry property will not hold

good. Insisting on modeling asymmetric membranes with no particular symmetry under inversion of ϕ , we can write down a generalised $C(\phi) = \lambda\phi + \lambda_1\phi^3 + \lambda_2\phi^2$ (truncating up to ϕ^3). The new λ_2 -term evidently breaks the symmetry under the inversion $(h, \phi) \rightarrow (-h, -\phi)$. Model asymmetric membranes with a non-zero λ_2 but with $\lambda = 0 = \lambda_1$ have been studied theoretically in Ref. [25], which illustrates the possibility of both first and second order transitions and generic enhancement of membrane fluctuations near the second order transitions. In the more general case with non-zero λ, λ_1 and λ_2 , we expect a combination of the results from this work and Ref. [25] to emerge, including possibly a more complex phase diagram. While a full analysis is beyond the scope of the present work, nonetheless, the results of Ref. [25] together with those here strongly highlights the generic nature of enhancement of membrane fluctuations and the possibilities of both first and second order MPTs.

Some technical comments are in order now. In writing \mathcal{F} [Eq. (1)] we have neglected the geometric nonlinearities which arise from expanding $h(\mathbf{x})$ about the perfectly flat base plane in the Monge gauge, e.g., area element $dS = d^2x\sqrt{1 + (\nabla h)^2} \simeq d^2x[1 + (\nabla h)^2/2]$, and the mean curvature $c_{mean} = -\nabla^2 h + \frac{1}{2}\nabla^2 h(\nabla h)^2 + \partial_i h \partial_j h \partial_{ij} h$ for small fluctuations in h ; $i, j = x, y$. Inclusion of the above in (1), generate additional nonlinear terms. Again straight forward scaling analysis near CP directly yields that these geometric nonlinearities are all *irrelevant* (in a scaling sense) in the presence of the couplings u and λ_1 . Hence, to the leading order, the geometric nonlinearities should be subleading to the existing nonlinearities in (1). This justifies omission of the geometric nonlinearities in our analysis above. Furthermore, there are additional symmetric (invariant under $h \rightarrow -h$ and $\phi \rightarrow -\phi$) nonlinear terms coupling h and ϕ , e.g., $\phi^2(\nabla^2 h)^2$ (ignored here), which are of thermodynamic origin and generically present for both symmetric and asymmetric heterogeneous membranes. This is, however, irrelevant (in a scaling sense), similar to the geometric nonlinearities. Thus, this term leaves the critical properties of MPT and the associated membrane fluctuations in our model asymmetric membrane unaffected. Within our Hartree approximation, there are little qualitative differences between $\lambda\lambda_1 > 0$ and $\lambda\lambda_1 < 0$ (keeping $\tilde{u} > 0$ for both), except for the degree of enhancement of the membrane

fluctuations near the associated MPT. Whether this is indeed the case or whether there are indeed significant qualitative differences between the two cases that are missed by our low-order perturbation theory should be investigated by more elaborate calculations. Our results suggest that in the special case with $\lambda\lambda_1 < 0$ in (1), when the harmonic and anharmonic composition fluctuation contributions to κ_e nearly mutually cancel to the leading order, the geometric and other symmetric nonlinearities mentioned above should become relevant, and the long wavelength properties of an asymmetric heterogeneous membrane described by (1) should be identical to a symmetric heterogeneous membrane, as described in Ref. [26]. Whether or not this actually happens can be determined by more detailed calculations that are beyond the scope of this work. Nonetheless, we can conclude with reasonable confidence that near the MPTs, an asymmetric heterogeneous membrane is likely to be generally softer than the corresponding symmetric heterogeneous membrane with the same bare bending modulus. In addition, in symmetric membranes ($\lambda\lambda_1 = 0$) the critical behaviour of ϕ will be controlled by the u -term, and hence, Ising-like. This establishes the 2D Ising universality for the MPTs in symmetric heterogeneous membranes, consistent with the known experimental results [2].

Studies on the possibility of budding transitions (see, e.g., Ref. [27]) in our model and its relation to the divergence or suppression of membrane fluctuations at CPs should be interesting. Time-dependent phenomena in our model, e.g., dynamic scaling and growth of order after a temperature quench through CPs, TP or first order transitions should be of interest from experimental point of views. Our work should be useful in the context of static and dynamic properties of phase transitions in Langmuir monolayers of polar molecules [28]. We hope our results will stimulate further theoretical and experimental works along these directions.

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